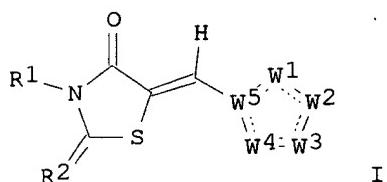


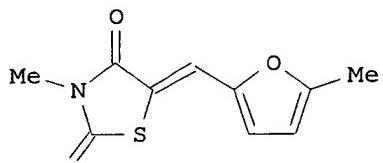
=> d 1-40 bib,abs

L7 ANSWER 1 OF 40 CA COPYRIGHT 2000 ACS
AN 133:30722 CA
TI Preparation of arylmethylene and heterocyclomethylene thiazolidinediones and analogs as tumor necrosis factor inhibitors
IN Wang, Jing; Ramnarayan, Kalyanaraman; Rideout, Darryl; Mong, Seymour;
Zhu, Hengyi; Niemeyer, Christina; Brady, Thomas P.
PA Structural Bioinformatics Inc., USA
SO PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000032598	A1	20000608	WO 1999-US28856	19991206
W: AU, CA, JP RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRAI US 1998-206108		19981204		
US 1999-316415		19990521		
OS MARPAT 133:30722				
GI				



I



II

AB The title compds. (I) [wherein W1-W5 together = aliph., heterocyclic, or heteroarom. ring; R1 = H or (un)substituted heterocyclic, (hetero)arom., or (cyclo)alkyl; R2 = O or S] and analogs were prep'd. by condensing aldehydes with thiazolidinediones. For example, 5-methylfuran-2-carboxaldehyde was coupled with 2-thioxo-3-methylthiazolidin-4-one to yield (E)-II (56%). I are TNF receptor antagonists that act as specific inhibitors of TNF-dependent NF-.kappa.B activation signaled by certain members of the TNF receptor superfamily for the prophylaxis and treatment of inflammatory diseases (no data).

RE.CNT 1

RE

(1) Texas Biotechnology Corporation; WO 9853790 A2 1998 CA

L7 ANSWER 2 OF 40 CA COPYRIGHT 2000 ACS
AN 133:26863 CA
TI Compositions and methods using PPAR gamma agonists for the treatment of Alzheimer's disease, central nervous system injury, and inflammatory diseases
IN Landreth, Gary; Combs, Colin; Silver, Jerry; Fitch, Michael T.
PA Case Western Reserve University, USA
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
------------	------	------	-----------------	------

PI WO 2000032190 A1 20000608 WO 1999-US27987 19991124
W: AU, CA, IL, JP, KR
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE

PRAI US 1998-200700 19981127

AB Methods and compns. using PPAR.gamma. agonists are provided for treating Alzheimer's disease and other diseases and conditions with an inflammatory

component (e.g., central nervous system injury). In particular, the invention provides PPAR.gamma. agonist agents that regulate the prodn. of proinflammatory and neurotoxic products involved in Alzheimer's disease and other diseases and conditions with an inflammatory component.

RE.CNT 3

RE

- (1) Bue-Valleskey; US 5716975 A 1998
- (2) Friedman; US 5607967 A 1997
- (3) Wilkerson; US 5326770 A 1994 CA

L7 ANSWER 3 OF 40 CA COPYRIGHT 2000 ACS

AN 132:202817 CA

TI Activation of peroxisome proliferator-activated receptor .gamma. does not inhibit IL-6 or TNF-.alpha. responses of macrophages to lipopolysaccharide

in vitro or in vivo

AU Thieringer, Rolf; Fenyk-Melody, Judy E.; Le Grand, Cheryl B.; Shelton, Beverly A.; Detmers, Patricia A.; Somers, Elizabeth P.; Carbin, Linda; Moller, David E.; Wright, Samuel D.; Berger, Joel

CS Departments of Endocrinology and Chemical Biology, Merck Research Laboratories, Rahway, NJ, 07065, USA

SO J. Immunol. (2000), 164(2), 1046-1054

CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists

DT Journal

LA English

AB The authors investigated the potential use of peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) agonists as anti-inflammatory agents in cell-based assays and in a mouse model of endotoxemia. Human peripheral blood monocytes were treated with LPS or PMA and a variety of PPAR.gamma. agonists. Although

15-deoxy-.DELTA.12,14-prostaglandin J2 (15d-PGJ2) at micromolar concns. inhibited the prodn. of TNF-.alpha. and IL-6, 4 other high affinity PPAR.gamma. ligands failed to affect cytokine prodn. Similar results were obtained when the monocytes were allowed to differentiate in culture into macrophages that expressed higher levels of PPAR.gamma. or when the murine macrophage cell line RAW 264.7 was used. Furthermore, satg. concns. of a potent PPAR.gamma.

ligand

not only failed to block cytokine prodn., but also were unable to block the inhibitory activity of 15d-PGJ2. Thus, activation of PPAR.gamma.

does

not appear to inhibit the prodn. of cytokines by either monocytes or macrophages, and the inhibitory effect obsd. with 15d-PGJ2 is most likely mediated by a PPAR.gamma.-independent mechanism. To examine the anti-inflammatory activity of PPAR.gamma. agonists in vivo, db/db mice were treated with a potent thiazolidinedione that lowered their elevated blood glucose and triglyceride levels as expected. When thiazolidinedione-treated mice were challenged with LPS, they displayed

no

suppression of cytokine prodn. Rather, their blood levels of TNF-.alpha. and IL-6 were elevated beyond the levels obsd. in control db/db mice challenged with LPS. Comparable results were obtained with the corresponding lean mice. Thus, compds. capable of activating PPAR.gamma. in leukocytes will not be useful for the treatment of acute inflammation.

RE.CNT 44

RE

- (1) Berger, J; Endocrinology 1996, V137, P4189 CA
- (2) Berger, J; J Biol Chem 1999, V274, P6718 CA
- (3) Berliner, J; Circulation 1995, V91, P2488 CA
- (6) Brun, R; Genes Dev 1996, V10, P974 CA
- (7) Chinetti, G; J Biol Chem 1998, V273, P25573 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 40 CA COPYRIGHT 2000 ACS

AN 133:12615 CA

TI Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-.gamma. activators

AU Pasceri, Vincenzo; Wu, Henry D.; Willerson, James T.; Yeh, Edward T. H.

CS Department of Internal Medicine, Texas Heart Institute, University of Texas Health Science Center, St Luke's Episcopal Hospital, Houston, TX, USA

SO Circulation (2000), 101(3), 235-238

CODEN: CIRCAZ; ISSN: 0009-7322

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.) is expressed in atherosclerotic plaques and in endothelial cells. The possible effects of PPAR.gamma. activators on endothelial activation and inflammatory response within the plaque are currently unknown. We tested the hypothesis that PPAR.gamma. activators inhibit vascular cell adhesion mol. (VCAM-1) and intercellular adhesion mol. (ICAM-1) expression in cultured endothelial cells (evaluated by flow cytometry) and homing of monocyte/macrophages to atherosclerotic plaques in vivo. In endothelial cells, the PPAR.gamma. agonists troglitazone at 100 .mu.mol/L and 15-deoxy-.DELTA.12,14-prostaglandin J2 (15d-PGJ2) at 20 .mu.mol/L

markedly

attenuated the tumor necrosis factor-induced expression of VCAM-1 and ICAM-1. A significant inhibition of VCAM-1 expression was also evident

at

5 and 10 .mu.mol/L 15d-PGJ2 and 20 .mu.mol/L troglitazone. Expression of E-selectin and PECAM-1 was not altered. To confirm the biol. relevance

of

these results, we assessed the effects of troglitazone on monocyte/macrophage homing to atherosclerotic plaques in apoE-deficient mice. A 7-day treatment with troglitazone (400 mg/kg) significantly reduced monocyte/macrophage homing to atherosclerotic plaques (236.+- .77 vs. 177.+- .43 macrophages, P=0.03); an even more striking inhibition was found at 3200 mg/kg troglitazone (344.+- .76 vs. 172.+- .83 macrophages, P=0.005). PPAR.gamma. activators inhibit expression of VCAM-1 and ICAM-1 in activated endothelial cells and significantly reduce monocyte/macrophage homing to atherosclerotic plaques. These findings suggest that PPAR.gamma. activators, currently used in treatment of type II diabetes, may have beneficial effects in modulating inflammatory response in atherosclerosis.

RE.CNT 18

RE

- (1) Berliner, J; Circulation 1995, V91, P2488 CA
- (2) Bishop-Bailey, D; J Biol Chem 1999, V274, P17042 CA
- (3) Bombeli, T; Blood 1997, V89, P2429 CA
- (4) Delerive, P; Circ Res 1999, V85, P394 CA
- (6) Fujiwara, T; Diabetes 1988, V37, P1549 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 40 CA COPYRIGHT 2000 ACS

AN 132:274109 CA

TI Inhibitory effect of troglitazone on tumor necrosis factor alpha-induced expression of monocyte chemoattractant protein-1 in human mesangial cells

AU Ohta, Masayoshi Y.; Nagai, Yukihiro; Takamura, Toshinari; Nohara, Erika; Kobayashi, Ken-Ichi

CS First Department of Internal Medicine, School of Medicine, Kanazawa University, Ishikawa, 920-8641, Japan
SO Metab., Clin. Exp. (2000), 49(2), 163-166
CODEN: METAAJ; ISSN: 0026-0495
PB W. B. Saunders Co.
DT Journal
LA English
AB Insulin resistance is one of the risk factors for the progression of atherosclerosis and glomerulosclerosis. Recently, the new oral insulin-sensitizing agent troglitazone has been thought to offer potential in the treatment of diabetes. If adopted for this use, it might be helpful in protecting against the development of atherosclerosis and microvascular complications via its improvement of insulin resistance. However, it has not yet been clarified whether troglitazone acts directly on the vascular cells and inhibits the progression of atherosclerosis, including glomerulosclerosis. Meanwhile, monocyte chemoattractant protein-1 (MCP-1) is known to play an important role in the pathogenesis of atherosclerosis and glomerulosclerosis through the induction of monocyte migration. Therefore, we investigated the effect of troglitazone on the expression of MCP-1 in human mesangial cells (HMCs). HMCs were treated with or without troglitazone (1 or 10 μ .mol/L) in the presence or absence of tumor necrosis factor alpha (TNF-.alpha.) at various concns. (50 or 500 ng/mL), and then MCP-1 secretion from the HMCs was measured. We found that TNF-.alpha. increased the secretion of MCP-1 by 55-fold vs. the control and troglitazone significantly inhibited this TNF-.alpha.-induced increase in MCP-1 secretion (49.3%). Moreover, Northern blot anal. showed that troglitazone decreased the MCP-1 mRNA level in HMCs. We demonstrated that .alpha.-tocopherol also inhibited TNF-.alpha.-induced MCP-1 prodn. in HMCs, although its effects were not as strong as troglitazone. The present study indicates that troglitazone may prevent the progression of atherosclerosis by inhibiting MCP-1 expression in mesangial cells.

RE.CNT 31
RE
(1) Chomczynski, P; Anal Biochem 1987, V162, P156 CA
(3) Fujii, M; Metabolism 1997, V46, P981 CA
(7) Hotamisligil, G; Science 1996, V271, P665 CA
(8) Jiang, C; Nature 1998, V391, P82 CA
(9) Kumar, S; Diabetologia 1996, V39, P701 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 40 CA COPYRIGHT 2000 ACS
AN 133:99385 CA
TI Down-regulation by troglitazone of hepatic tumor necrosis factor-.alpha. and interleukin-6 mRNA expression in a murine model of non-insulin-dependent diabetes
AU Sigrist, S.; Bedoucha, M.; Boelsterli, U. A.
CS Department of Non-Clinical Drug Safety, F. Hoffmann-La Roche AG, Basel, CH-4070, Switz.
SO Biochem. Pharmacol. (2000), 60(1), 67-75
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Troglitazone, a novel thiazolidinedione drug used to treat non-insulin-dependent diabetes mellitus, is a selective ligand for the peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.). Recent results indicate that PPAR.gamma. activation by thiazolidinediones regulates adipose tissue- and monocyte/peritoneal macrophage-derived cytokine expression in vitro. We evaluated whether troglitazone may also

neg. regulate cytokine expression in the liver, which harbors the majority of the body's resident macrophages but which only weakly expresses PPAR.gamma.. Lean C57BL6 mice and genetically obese KKAY mice were chronically treated with troglitazone (100 mg/kg/day for 2 wk). At the end of treatment, hepatic expression of tumor necrosis factor (TNF)-.alpha. and interleukin (IL)-6 mRNA was quant. detd. by kinetic polymerase chain reaction both under basal conditions and after stimulation with lipopolysaccharide (LPS). Both untreated lean and obese mice exhibited low levels of baseline TNF-.alpha. and IL-6 mRNA expression and responded with a dramatic increase in hepatic cytokine transcripts and TNF-.alpha. protein expression following a challenge with LPS. Similar to the effects on white adipose tissue, troglitazone not only down-regulated the baseline levels of hepatic TNF-.alpha. and IL-6, but also greatly attenuated the inducing effects of LPS. The extent of this inhibitory effect of troglitazone was higher in obese KKAY mice than in lean mice and was also reflected by markedly down-regulated hepatic TNF-.alpha. protein expression. These data demonstrate that chronic administration of troglitazone is assocd. with a greatly attenuated responsiveness towards inducers of hepatic TNF-.alpha. and IL-6 prodn. The possible biol. consequences of these effects, however, have not yet been assessed.

RE.CNT 44

RE

- (1) Bradford, M; Anal Biochem 1976, V72, P248 CA
- (3) Castle, C; Arterioscler Thromb 1993, V13, P302 CA
- (6) Decker, K; Eur J Biochem 1990, V192, P245 CA
- (7) Decker, T; J Immunol 1987, V138, P957 CA
- (9) Fajas, L; J Biol Chem 1997, V272, P18779 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 40 CA COPYRIGHT 2000 ACS

AN 131:281581 CA

TI Methods using a modulator of a MAPK/ERK, JNK, or p38 signal transduction pathway for treating and preventing insulin resistance and related disorders

IN Greenberg, Andrew S.

PA Trustees of Tufts College, USA

SO PCT Int. Appl., 80 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9953927	A1	19991028	WO 1999-US8364	19990416

W: JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE

PRAI US 1998-82152 19980417
US 1998-82741 19980423

AB The invention provides methods, therapeutics, and kits for treating and preventing diseases or conditions assocd. with excessive lipolysis, in particular TNF-.alpha. induced lipolysis, and/or excessive free fatty acid

levels. Exemplary conditions include insulin-resistance, diabetes (in particular, non-insulin-dependent diabetes mellitus), obesity, glucose intolerance, hyperinsulinemia, polycystic ovary syndrome, and coronary artery disease. In a preferred embodiment, the method includes administering to a subject in need a pharmaceutically effective amt. of an inhibitor of the JNK signal transduction pathway and/or an inhibitor of

the MAPK/ERK signal transduction pathway and/or a stimulator of the p38 signal transduction pathway.

RE.CNT 13

RE

- (2) Font De Mora, J; Mol Cell Biol 1997, V17(10), P6068 CA
- (4) Kliewer; Cell 1995, V83, P813 CA
- (5) Pearson; Biochem Biophys Res Commun 1996, V229, P752 CA
- (6) Sale; EMBO J 1995, V14(4) CA
- (7) Schoenhoefer, P; Biochem Pharmacol 1973, V22, P629 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 40 CA COPYRIGHT 2000 ACS

AN 131:199620 CA

TI Preparation of indole derivatives as phospholipase enzyme inhibitors
IN Seehra, Jasbir S.; Xiang, Yibin; Bemis, Jean; McKew, John; Kaila, Neelu;
Chen, Lihren

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 225 pp.

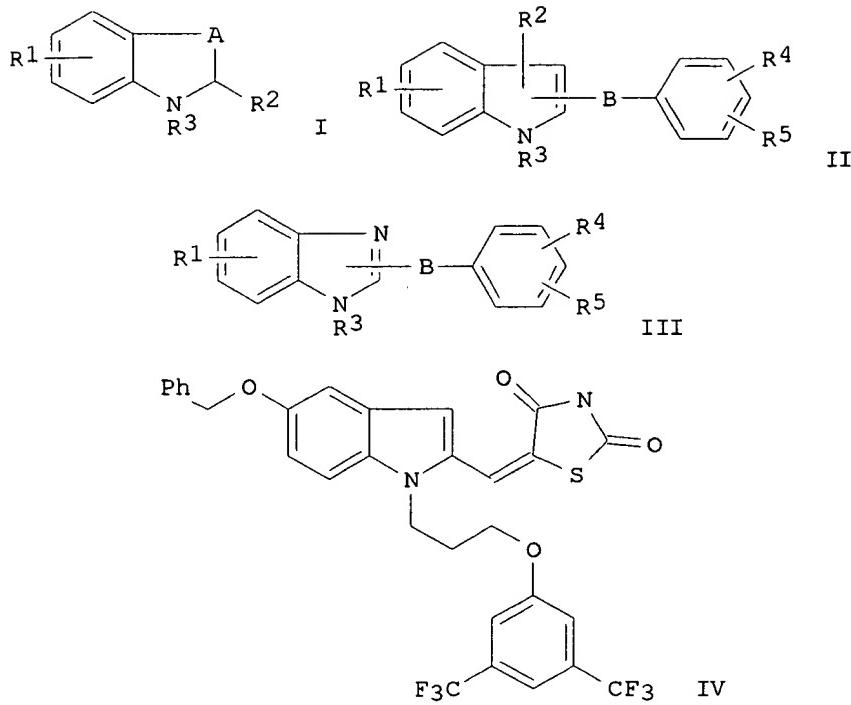
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9943672	A1	19990902	WO 1999-US3388	19990217
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9932970	A1	19990915	AU 1999-32970	19990217
PRAI	US 1998-30102		19980225		
	WO 1999-US3388		19990217		
OS	MARPAT	131:199620			
GI					



AB Indole derivs. (I), (II), and (III) [where A = CH₂ or CH₂CH₂; B = (CH₂)_n, (CH₂O)_n, (CH₂S)_n, (OCH₂)_n, (SCH₂)_n, (CH=CH)_n, (C.tplbond.C)_n, CON(R₆), N(R₆)CO, O, S, or N(R₆); R₁ and R₅ = independently H, OH, halogen, CN, NO₂, C₁₋₅ alkyl, alkenyl, alkynyl, or (un)substituted aryl, etc.; R₂ and R₃ = independently H, CO₂H, COR₅, CONR₅R₆, (CH₂)_nW(CH₂)_mZR₅, (CH₂)_nWR₅, ZR₅, C₁₋₁₀ alkyl, alkenyl, or substituted aryl; R₄ = H, OH, OR₆, SR₆, CN, COR₆, NHR₆, CO₂H, COR₆R₇, NO₂, (un)substituted sulfamidocarbonyl, C₁₋₅ alkyl, alkenyl, or substituted aryl; R₆, R₇ = H, C₁₋₅ alkyl, alkenyl, alkynyl, or (un)substituted aryl; W = O, S, CH₂, CH=CH, C.tplbond.C, or N(R₆); X = O, S, N(R₆), CO, CON(R₆), N(R₆)CO; m and n = independently 0-4] and pharmaceutically acceptable salts thereof,

were

prepd. Thus, 2,4-thiazolidinedione and K₂CO₃ followed by NaOH were added to

5-(benzyloxy)-1-(4-([3,5-bis(trifluoromethyl)phenoxy]methyl)benzyl)-1H-indole-2-carboxaldehyde in EtOH to form the 2,4-thiazolidinedion-4-ylidene

deriv. The ylidene was dissolved in a soln. of DMF and NaH, reacted with an alkyl ester of 4-(bromomethyl)benzoic acid, and deesterified with HF to

yield the acid, (E)-(IV). The title compds. are useful as phospholipase enzyme inhibitors, esp. cytosolic phospholipase A₂ (cPLA₂), for treatment of inflammatory conditions, particularly where inhibition of prodn. of prostaglandins, leukotrienes, and PAF are all desired. Eighty-seven compds. of the invention were tested for phospholipase enzyme inhibiting activity in the LysoPC and/or Coumarine assay. IC₅₀ values ranged from 0.081 .mu.M to >50 .mu.M for the LysoPC assay and from 2.5 .mu.M to >64 .mu.M for the Coumarine assay. Selected compds. were tested for in vivo activity in the carrageenan-induced rat paw edema test, and showed 4.2% to

34.2% inhibition. Forty-eight compds. of the invention were tested for cPLA₂ enzyme activity, and exhibited 25% to 95% inhibition at concns. of

3

.mu.M to 100 .mu.M.

RE.CNT 5

RE

(1) Eli Lilly And Company; EP 0620215 A 1994

- (2) Genetics Institute Inc; WO 9808818 A 1998
 (3) Merckle GmbH; WO 9805637 A 1998
 (4) Merckle GmbH Chem -Pharm Fabrik; WO 9513266 A 1995
 (5) Shionogi & Co Ltd; WO 9705135 A 1997

L7 ANSWER 9 OF 40 CA COPYRIGHT 2000 ACS

AN 131:199619 CA

TI Preparation of indole derivatives as phospholipase enzyme inhibitors

IN Seehra, Jasbir S.; McKew, John C.; Lovering, Frank; Bemis, Jean E.;

Xiang,

Yibin; Chen, Lihren; Knopf, John L.

PA Genetics Institute, Inc., USA

SO PCT Int. Appl., 182 pp.

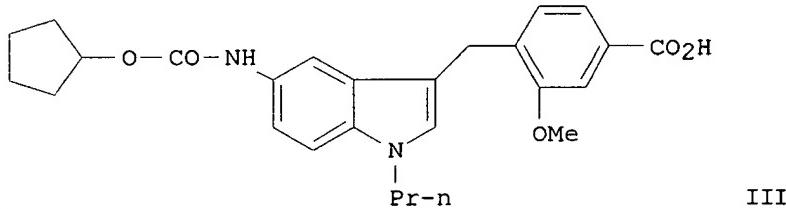
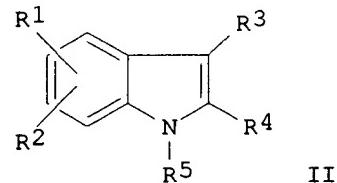
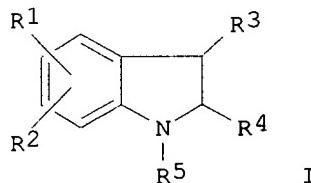
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9943654	A2	19990902	WO 1999-US3898	19990224
	WO 9943654	A3	19991028		
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,			
TM	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9927825	A1	19990915	AU 1999-27825	19990224
PRAI	US 1998-30592		19980225		
	WO 1999-US3898		19990224		
OS	MARPAT	131:199619			
GI					



AB Indole derivs. (I) and (II) [where R¹ = H, halogen, C₁-10 alkyl, S-C₁-10 alkyl, C₁-10 alkoxy, CN, NO₂, NH₂, Ph, OPh, SPh, CH₂Ph, OCH₂Ph, SCH₂Ph, or (un)substituted amido, carbamido, sulfonyl, etc.; R² = H, halogen, CF₃, OH, C₁-10 alkyl, C₁-10 alkoxy, CHO, CN, NO₂, (un)substituted amino, SO₂-C₁-6 alkyl; R³ = (un)substituted carboxylic acid, OPO₃H₂, SO₃H, etc.; R⁴ = H, CF₃, C₁-6 alkyl, C₁-6 alkoxy, (C₁-6 alkyl)cycloalkyl, CHO,

halogen, etc.; R5 = C1-6 alkyl, C1-6 alkoxy, (C1-6 alkyl)cycloalkyl,
etc.]

and pharmaceutically acceptable salts thereof, were prep'd. by several methods. Thus, 5-nitroindole was C3-alkylated with Me 4-(bromomethyl)-3-methoxybenzoate in dioxane, N-alkylated with 1-iodopropane in a soln. of THF and NaH, and converted to the amine by hydrogenation over Pt/C. The amine was converted to the carbamate by addn. of cyclopentyl chloroformate in CH₂Cl₂ and 4-methylmorpholine and the resultant ester hydrolyzed to yield 4-[{(5-[(cyclopentyloxy)carbonyl]amino)-1-propyl-1H-indol-3-yl)methyl]-3-methoxybenzoic acid (III). The title compds. are useful as phospholipase enzyme inhibitors, esp. cytosolic phospholipase A2 (cPLA2), for treatment of inflammatory conditions, particularly where inhibition of prodn. of prostaglandins, leukotrienes, and PAF are all desired. Over one hundred compds. of the invention were tested for cPLA2 inhibiting activity in the Coumarine assay and rat carrageenan-induced footpad edema test. Compds. exhibited 7% to 98% inhibition at concns. of 0.125 .mu.M to 400 .mu.M in the Coumarine assay and -7.16% to 34.52% inhibition at concns. of 2 .mu.M to 20 .mu.M in the footpad edema test.

L7 ANSWER 10 OF 40 CA COPYRIGHT 2000 ACS

AN 130:205119 CA

TI TNF-.alpha. inhibitors as anti-inflammatory agents

IN Odaka, Hiroyuki; Momose, Yu

PA Takeda Chemical Industries, Ltd., Japan

SO PCT Int. Appl., 32 pp.

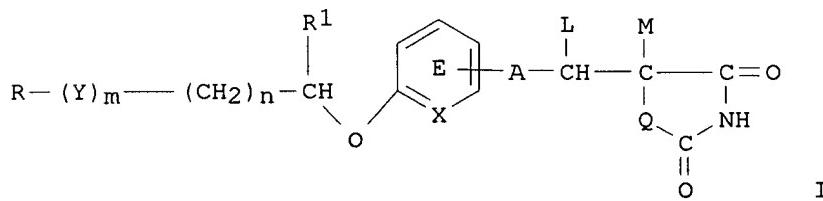
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9909965	A2	19990304	WO 1998-JP3692	19980820
	WO 9909965	A3	19990520		
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9887479	A1	19990316	AU 1998-87479	19980820
	JP 11124331	A2	19990511	JP 1998-234750	19980820
	EP 1007038	A2	20000614	EP 1998-938913	19980820
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	JP 1997-225302		19970821		
	WO 1998-JP3692		19980820		
OS	MARPAT	130:205119			
GI					



AB An antiinflammatory agent, which affects by way of a TNF-.alpha. (tumor necrosis factor .alpha.) inhibitory action, comprises thiolidinedione analogs [I; R = (un)substituted hydrocarbon or heterocyclic group; Y = CO,

CH(OH), NR3; R3 = (un)substituted alkyl group; m = 0, 1; n = 0, 1, 2; X = CH, N; A = chem. bond, bivalent C1-7 aliph. hydrocarbon group; Q = O, S; R1 = H, alkyl group; ring E may have further 1-4 substituents, which may form a ring in combination with R1; L, M = H or combined with each other to form a chem. bond] or a salt thereof. A tablet contg. pioglitazone.cntdot.HCl 16.53, lactose 92.87, Ca CMC 7.2, hydroxypropyl cellulose 3, and Mg stearate 0.4 mg was prep'd. and its TNF-.alpha. inhibitory activities were tested using mice and rats.

L7 ANSWER 11 OF 40 CA COPYRIGHT 2000 ACS

AN 131:317812 CA

TI Methods for treating proliferative and inflammatory skin diseases with a modulator of PPAR.gamma.

IN Pershad Singh, Harrihar A.

PA USA

SO U.S., 13 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5981586	A	19991109	US 1998-84037	19980522
PRAI US 1997-47550		19970523		

AB Methods of inhibiting the proliferation of keratinocytes and inflammation of the skin are disclosed which comprise administering to a human in need of treatment an effective amt. of a compd., or a pharmaceutically acceptable salt or solvate thereof, that modifies the activity of the peroxisome proliferator-activated receptor gamma (PPAR.gamma.) in skin.

RE.CNT 3

RE

(1) Anon; WO 9535108 A1 1995 CA

(2) Anon; WO 9609055 A1 1996 CA

(3) Cunliffe; Brit J Dermatol 1969, V81(10), P280

L7 ANSWER 12 OF 40 CA COPYRIGHT 2000 ACS

AN 131:335343 CA

TI Cellular and molecular mechanisms of glial scarring and progressive cavitation: in vivo and in vitro analysis of inflammation-induced secondary injury after CNS trauma

AU Fitch, Michael T.; Doller, Catherine; Combs, Colin K.; Landreth, Gary E.; Silver, Jerry

CS Department of Neurosciences and Alzheimer Research Laboratory, Case Western Reserve University School of Medicine, Cleveland, OH, 44106, USA

SO J. Neurosci. (1999), 19(19), 8182-8198

CODEN: JNRSDS; ISSN: 0270-6474

PB Society for Neuroscience

DT Journal

LA English

AB Post-traumatic cystic cavitation, in which the size and severity of a CNS injury progress from a small area of direct trauma to a greatly enlarged secondary injury surrounded by glial scar tissue, is a poorly understood complication of damage to the brain and spinal cord. Using minimally invasive techniques to avoid primary phys. injury, this study demonstrates

in vivo that inflammatory processes alone initiate a cascade of secondary tissue damage, progressive cavitation, and glial scarring in the CNS. An in vitro model allowed us to test the hypothesis that specific mols. that stimulate macrophage inflammatory activation are an important step in initiating secondary neuropathol. Time-lapse video analyses of inflammation-induced cavitation in our in vitro model revealed that this process occurs primarily via a previously undescribed cellular mechanism involving dramatic astrocyte morphol. changes and rapid migration. The phys. process of cavitation leads to astrocyte abandonment of neuronal processes, neurite stretching, and secondary injury. The macrophage

mannose receptor and the complement receptor type 3 .beta.2-integrin are implicated in the cascade that induces cavity and scar formation. We also demonstrate that anti-inflammatory agents modulating transcription via the nuclear hormone receptor peroxisome proliferator-activated receptor-.gamma. may be therapeutic in preventing progressive cavitation by limiting inflammation and subsequent secondary damage after CNS injury.

RE.CNT 70

RE

- (2) Elenius, K; J Cell Biol 1991, V114, P585 CA
- (3) Engering, A; Eur J Immunol 1997, V27, P2417 CA
- (4) Faassen, A; J Cell Biol 1992, V116, P521 CA
- (5) Faber-Elman, A; J Clin Invest 1996, V97, P162 CA
- (6) Fitch, M; CNS regeneration: basic science and clinical advances 1999, P55 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 40 CA COPYRIGHT 2000 ACS

AN 131:295416 CA

TI Troglitazone can prevent development of type 1 diabetes induced by multiple low-dose streptozotocin in mice

AU Ogawa, Junko; Takahashi, Sayaka; Fujiwara, Toshihiko; Fukushige, Junichiro; Hosokawa, Tsunemichi; Izumi, Takashi; Kurakata, Shinichi; Horikoshi, Hiroyoshi

CS Pharmacology & Molecular Biology and Biological Res. Labs, Sankyo Co, Tokyo, 140, Japan

SO Life Sci. (1999), 65(12), 1287-1296
CODEN: LIFSAK; ISSN: 0024-3205

PB Elsevier Science Inc.

DT Journal

LA English

AB Cytotoxic cytokines, such as tumor necrosis factor (TNF)-.alpha. and interleukin (IL)-1.beta., or free radicals may play a role in the destruction of pancreatic .beta.-cells in type 1 diabetes mellitus. Antioxidant or anti-TNF.alpha. and IL-1.beta. therapy could prevent the development of type I diabetes. Troglitazone is an antidiabetic agent with the ability to enhance the insulin action via activating peroxisome proliferator-activated receptors .gamma. (PPAR.gamma.) and to scavenge free radicals. We examd. the effects of troglitazone on the development of type 1 diabetes mellitus in DBA/2 mice given multiple low doses of streptozotocin (MLDSTZ). The effects of troglitazone on cytokine-induced pancreatic .beta.-cell damage were examd. in vitro. Type 1 diabetes was induced by MLDSTZ at 40 mg/kg/day i.p. for 5 days. Troglitazone was given

in feed at 0.2% (240 mg/kg/day) for 4 wk from the start of or immediately after the STZ injections. STZ elevated blood plasma glucose levels to 615.+-8 mg/dL at 4 wk after the final STZ injection; the effect was accompanied by infiltration of leukocytes in pancreatic islets (insulitis). Troglitazone combined with MLDSTZ prevented hyperglycemia (230.+-30 mg/dL) and suppressed insulitis and in vitro TNF.alpha. prodn. from i.p. exudate cells. TNF.alpha. (10 pg/mL) and IL-1.beta. (1 pg/mL) addn. to hamster insulinoma cell line HIT-T15 for 7 days in vitro decreased the insulin secretion and cell viability. Simultaneous troglitazone addn. (0.03-3 .mu.M) improved the cytokine-induced decrease in insulin secretion and cell viability. Thus, troglitazone prevents the development of type 1 diabetes mellitus in the MLDSTZ model by suppressing

insulitis assocd. with decreasing TNF.alpha. prodn. from i.p. exudate cells and the subsequent TNF.alpha. and IL-1.beta.-induced .beta.-cell damage.

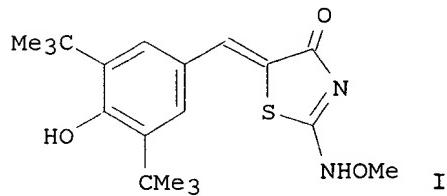
RE.CNT 30

RE

- (2) Beales, P; Hor Met Res 1994, V26, P450 CA

- (3) Fujiwara, T; Diabetes 1988, V37, P1549 CA
 (4) Hayward, A; J Lab Clin Med 1992, V119, P503 CA
 (5) Heineke, E; Diabetes 1993, V42, P1721 CA
 (6) Horikoshi, H; JP 07285864 1995 CA
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 40 CA COPYRIGHT 2000 ACS
 AN 130:252279 CA
 TI Synthesis, structure-activity relationships, and in vivo evaluations of substituted di-tert-butylphenols as a novel class of potent, selective, and orally active cyclooxygenase-2 inhibitors. 1. Thiazolone and oxazolone series
 AU Song, Yuntao; Connor, David T.; Doubleday, Robert; Sorenson, Roderick J.; Serpel, Anthony D.; Unangst, Paul C.; Roth, Bruce D.; Gilbertsen, Richard B.; Chan, Kam; Schrier, Denis J.; Guglietta, Antonio; Bornemeier, Dirk A.; Dyer, Richard D.
 CS Departments of Chemistry Biochemistry and Immunopathology, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI, 48105, USA
 SO J. Med. Chem. (1999), 42(7), 1151-1160
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 GI



AB Selective cyclooxygenase-2 (COX-2) inhibitors have been shown to be potent antiinflammatory agents with fewer side effects than currently marketed nonsteroidal antiinflammatory drugs (NSAIDs). Initial mass screening and subsequent structure-activity relationship (SAR) studies have identified benzylidenethiazolone I (PD138387) as the most potent and selective COX-2 inhibitor within the thiazolone and oxazolone series of di-tert-butylphenols. Compd. I has an IC₅₀ of 1.7 .mu.M against recombinant human COX-2 and inhibited COX-2 activity in the J774A.1 cell line with an IC₅₀ of 0.17 .mu.M. It was inactive against purified ovine COX-1 at 100 .mu.M and did not inhibit COX-1 activity in platelets at 20 .mu.M. Compd. I was also orally active in vivo with an ED₄₀ of 16 mg/kg in the carrageenan footpad edema (CFE) assay and caused no gastrointestinal (GI) damage in rats at the dose of 100 mg/kg but inhibited gastric prostaglandin E2 (PGE2) prodn. in rats' gastric mucosa by 33% following a dose of 100 mg/kg. The SAR studies of this chem. series revealed that the potency and selectivity are very sensitive to minor structural changes. A simple isosteric replacement led to the reversal of selectivity.

- RE.CNT 34
 RE
 (2) Barnett, J; Biochim Biophys Acta 1994, V1209, P130 CA
 (4) Cetenko, W; EP 343643 1989 CA
 (5) Cetenko, W; EP 449216 1991 CA

- (6) Chan, C; J Pharmacol Exp Ther 1995, V274, P1531 CA
(7) Ferreira, S; Nature (New Biol) 1971, V231, P237 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 40 CA COPYRIGHT 2000 ACS
AN 131:69224 CA
TI Down regulation of peroxisome proliferator-activated receptor .gamma.
expression by inflammatory cytokines and its reversal by
thiazolidinediones
AU Tanaka, T.; Itoh, H.; Doi, K.; Fukunaga, Y.; Hosoda, K.; Shintani, M.;
Yamashita, J.; Chun, T.-H.; Inoue, M.; Masatsugu, K.; Sawada, N.; Saito,
T.; Inoue, G.; Nishimura, H.; Yoshimasa, Y.; Nakao, K.
CS Department Medicine Clinical Science, Graduate School Medicine, Kyoto
Univ., Kyoto, 606, Japan
SO Diabetologia (1999), 42(6), 702-710
CODEN: DBTGAJ; ISSN: 0012-186X
PB Springer-Verlag
DT Journal
LA English
AB Previous studies show that inflammatory cytokines play a part in the
development of insulin resistance. Thiazolidinediones were developed as
insulin-sensitizing drugs and are ligands for the peroxisome
proliferator-activated receptor .gamma. (PPAR.gamma.). The authors
hypothesized that the anti-diabetic mechanism of thiazolidinediones
depends on the quantity of PPAR.gamma. in the insulin resistant state in
which inflammatory cytokines play a part. The authors isolated rat
PPAR.gamma.1 and .gamma.2 cDNAs and examined effects of various cytokines
and thiazolidinediones on PPAR.gamma. mRNA expression in rat mature
adipocytes. Various inflammatory cytokines, such as tumor necrosis
factor-.alpha. (TNF-.alpha.), interleukin(IL)-1.alpha., IL-1.beta., IL-6,
and leukemia inhibitory factor decreased PPAR gamma mRNA expression. H2O2,
lysophosphatidylcholine, or phorbol 12-myristate 13-acetate also
decreased
the expression of PPAR.gamma.. The suppression of PPAR.gamma. mRNA
expression caused by 10 nmol/L TNF-.alpha. was reversed 60% and 55% by
10-4 mol/L troglitazone and 10-4 mol/L of pioglitazone, resp. The
suppression of glucose transporter 4 mRNA expression caused by
TNF-.alpha.
was also reversed by thiazolidinediones. Assoc'd. with the change of
PPAR.gamma. mRNA expression, troglitazone improved glucose uptake
suppressed by TNF-.alpha.. This study suggests that inflammatory
cytokines could be factors that regulate PPAR.gamma. expression for
possible modulation of insulin resistance. The authors speculate that
the
regulation of PPAR.gamma. mRNA expression may contribute to the
anti-diabetic mechanism of thiazolidinediones.

RE.CNT 39
RE
(3) Costa, G; Cancer Res 1977, V37, P2327 CA
(4) Czech, M; J Biol Chem 1974, V249, P5421 CA
(5) Elbrecht, A; Biochem Biophys Res Commun 1996, V224, P431 CA
(6) Fujiwara, T; Diabetes 1988, V37, P1549 CA
(7) Grunfeld, C; Biotherapy 1991, V3, P143 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 40 CA COPYRIGHT 2000 ACS
AN 131:194047 CA
TI Hypertension and insulin resistance: role of peroxisome
proliferator-activated receptor .gamma.
AU Itoh, Hiroshi; Doi, Kentaro; Tanaka, Tokuji; Fukunaga, Yasutomo; Hosoda,
Kiminori; Inoue, Gen; Nishimura, Haruhiko; Yoshimasa, Yasunao; Yamori,
Yukio; Nakao, Kazuwa
CS Department of Medicine and Clinical Science, Kyoto University Graduate
School of Medicine, Kyoto University, Kyoto, 606-8507, Japan
SO Clin. Exp. Pharmacol. Physiol. (1999), 26(7), 558-560

CODEN: CEXPB9; ISSN: 0305-1870

PB Blackwell Science Asia Pty Ltd.

DT Journal

LA English

AB 1. Insulin resistance has been highlighted as a common causal factor for hypertension, hyperlipidemia, diabetes mellitus and obesity, all of which are recognized to occur simultaneously, and a distinct clin. entity is defined as "multiple risk factor syndrome". 2. Recently, a new class of antidiabetic agents, thiazolidinediones (TZD) has been developed and has been shown to improve insulin resistance by binding and activating a nuclear receptor, peroxisome proliferator-activated receptor (PPAR).gamma.. 3. CDNA of rat PPAR.gamma.1 and .gamma.2 were cloned and gene regulation of PPAR.gamma. in rat mature adipocytes was exmd. Hydrogen peroxide, an oxygen radical, which is recognized to be the common

intracellular signal for multiple risk factors, potently down-regulated PPAR.gamma. mRNA expression in rat mature adipocytes. 4. Tumor necrosis factor (TNF)-.alpha., which is considered to play a role in obesity-induced non-insulin-dependent diabetes mellitus and to augment oxidative stress, also suppressed PPAR.gamma. expression. 5. Thiazolidinediones dose-dependently recovered TNF-.alpha.-induced down-regulation of PPAR.gamma. mRNA expression. 6. The modulation of PPAR.gamma. expression by TZD can be one mechanism for the improvement of insulin resistance by TZD. 7. Vascular tone and remodelling are controlled by several vasoactive autocrine/paracrine factors produced by endothelial cells in response to several vascular injury stimuli, including hypertension. The PPAR.gamma. gene transcript was detected in cultured endothelial cells. 8. The administration of TZD stimulated the endothelial secretion of type-C natriuretic peptide, which is one of the natriuretic peptide family and is demonstrated by the authors to act as a novel endothelium-derived relaxing peptide. 9. Concomitantly, TZD significantly suppressed the secretion of endothelin, a potent endothelium-derived vasoconstricting peptide. 10. Thiazolidinediones can affect vascular tone and growth by modulating the prodn. of endothelium-derived vasoactive substances to influence occurrence and progression of hypertension and atherosclerosis.

RE.CNT 21

RE

- (1) Chang, A; Diabetes 1983, V32, P830 CA
- (3) Doi, K; Biochem Biophys Res Commun 1997, V239, P889 CA
- (6) Forman, B; Cell 1995, V83, P803 CA
- (7) Fujita, T; Diabetes 1983, V32, P804 CA
- (8) Fujiwara, T; Diabetes 1988, V37, P1549 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 40 CA COPYRIGHT 2000 ACS

AN 131:266844 CA

TI A novel therapy for colitis utilizing PPAR-.gamma. ligands to inhibit the epithelial inflammatory response

AU Su, Chinyu G.; Wen, Xiaoming; Bailey, Shannon T.; Jiang, Wen; Rangwala, Shamina M.; Keilbaugh, Sue A.; Flanigan, Anne; Murthy, Sreekant; Lazar, Mitchell A.; Wu, Gary D.

CS Division of Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA

SO J. Clin. Invest. (1999), 104(4), 383-389

CODEN: JCINAO; ISSN: 0021-9738

PB American Society for Clinical Investigation

DT Journal

LA English

AB Peroxisome proliferator-activated receptor .gamma. (PPAR-.gamma.), a member of the nuclear hormone receptor super-family originally shown to play a crit. role in adipocyte differentiation and glucose homeostasis, has recently been implicated as a regulator of cellular proliferation and inflammatory responses. Colonic epithelial cells, which express high levels of PPAR-.gamma. protein, have the ability to produce inflammatory

cytokines that may play a role in inflammatory bowel disease (IBD). We report here that PPAR-.gamma. ligands dramatically attenuate cytokine gene

expression in colon cancer cell lines by inhibiting the activation of nuclear factor-.kappa.B via an I.kappa.B.-dependent mechanism. Moreover, thiazolidinedione ligands for PPAR-.gamma. markedly reduce colonic inflammation in a mouse model of IBD. These results suggest that colonic PPAR-.gamma. may be a therapeutic target in humans suffering from IBD.

RE.CNT 53

RE

- (1) Adams, M; J Biol Chem 1997, V272, P5128 CA
 - (2) Andoh, A; J Immunol 1993, V151, P4239 CA
 - (3) Auphan, N; Science 1995, V270, P286 CA
 - (5) Baribault, H; Genes Dev 1994, V8, P2964 CA
 - (6) Belluzzi, A; N Engl J Med 1996, V334, P1557 CA
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 40 CA COPYRIGHT 2000 ACS

AN 130:336720 CA

TI TNF-.alpha.-induced migration of vascular smooth muscle cells is MAPK dependent

AU Goetze, Stephan; Xi, Xiao-Ping; Kawano, Yasuko; Kawano, Hiroaki; Fleck, Eckart; Hsueh, Willa A.; Law, Ronald E.

CS Division of Endocrinology, Diabetes and Hypertension, University of California, Los Angeles, CA, USA

SO Hypertension (1999), 33(1, Pt. 2), 183-189

CODEN: HPRTDN; ISSN: 0194-911X

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Migration of vascular smooth muscle cells (VSMC) is a key event in neointimal formation and atherosclerosis that may be linked to the accumulation of inflammatory cells and release of chemotactic cytokines. Tumor necrosis factor-.alpha. (TNF-.alpha.) induces chemotaxis of inflammatory cells and fibroblasts, but little is known about chemotactic signaling by TNF-.alpha. in VSMC. The aim here was to investigate the role of TNF-.alpha. in VSMC migration and to elucidate the chemotactic signaling pathways mediating this action. TNF-.alpha. (50-400 U/mL) induced migration of cultured rat aortic VSMC in a dose-dependent manner. Because activation of the extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase (MAPK) is known to be required in platelet-derived growth factor-directed and angiotensin II-directed migration of these cells, the authors used the MAPK-inhibitor PD98059 to det. if chemotactic signaling by TNF-.alpha. involves the MAPK pathway as well. The authors found that TNF-.alpha.-directed migration was substantially inhibited by PD98059. TNF-.alpha. (100 U/mL) transiently activated MAPK with a maximal induction 10 min after stimulation that returned to baseline levels by 2 h after treatment. Only a single peak

of

increased MAPK activity was seen. PD98059 also blocked TNF-.alpha.-stimulated MAPK activation in a concn.-dependent manner,

which

is consistent with its inhibition of TNF-.alpha.-directed migration. To identify which TNF-.alpha. receptor is involved in TNF-.alpha.-induced MAPK activation, antibodies against the p55 TNF-.alpha. receptor-1 (TNF-R1) and the p75 TNF-.alpha. receptor-2 (TNF-R2) were used. VSMC express both receptors, but TNF-.alpha.-induced MAPK activation was inhibited only by the TNF-R1 antibody. The TNF-R2 antibody had no effect.

Thiazolidinediones are known to inhibit TNF-.alpha. signaling in adipose tissue and attenuate platelet-derived growth factor-directed and angiotensin II-directed migration in VSMC. The authors therefore investigated the effects of the thiazolidinediones troglitazone (TRO) and rosiglitazone (RSG) on TNF-.alpha.-induced migration. Both TRO and RSG

inhibited migration, but neither attenuated TNF-.alpha.-induced MAPK activation, indicating that their anti-migration activity was exerted downstream of MAPK. Thus, early activation of MAPK is a crucial event in TNF-.alpha.-mediated signal transduction leading to VSMC migration. Moreover, inhibition of TNF-.alpha.-directed migration by the insulin sensitizers TRO and RSG underscores their potential as vasculoprotective agents.

RE.CNT 46

RE

- (1) Abedi, H; Cardiovasc Res 1995, V30, P544 CA
- (2) Barath, P; Am J Pathol 1990, V137, P503 CA
- (3) Barbara, J; Immunol Cell Biol 1996, V74, P434 CA
- (4) Bilato, C; J Clin Invest 1995, V96, P1905 CA
- (5) Bilato, C; J Clin Invest 1997, V100, P693 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 40 CA COPYRIGHT 2000 ACS

AN 131:125251 CA

TI Inhibition of tumor necrosis factor-.alpha. with anti-diabetic agents
AU Fukuzawa, M.; Satoh, J.; Qiang, X.; Miyaguchi, S.; Sakata, Y.; Nakazawa,
T.; Ikehata, F.; Ohta, S.; Toyota, T.

CS Third Department of Internal Medicine, Tohoku University School of
Medicine, Sendai, Japan

SO Diabetes Res. Clin. Pract. (1999), 43(3), 147-154
CODEN: DRCPE9; ISSN: 0168-8227

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

AB It has recently been indicated that tumor necrosis factor-.alpha.
(TNF-.alpha.) prodn. is increased under chronic hyperglycemia and
TNF-.alpha. has harmful effects on insulin sensitivity and possibly on
chronic diabetic complications. Therefore it will be favorable for
diabetes treatment if anti-diabetic agents also have anti-TNF-.alpha.
activities. In this study, we have investigated effects of hypoglycemic
sulfonylureas (gliclazide and glibenclamide) and a thiazolidinedione
(troglitazone) on lipopolysaccharide-induced TNF-.alpha. prodn., which

was

evaluated by immunoassay and bioassay, in vivo using mice and partly in
vitro using human peripheral blood mononuclear cells. Gliclazide
significantly inhibited TNF-.alpha. prodn. in vivo and also in vitro at a
concn. of 10⁻³ mol/l. However, glibenclamide had neither effect on
TNF-.alpha. prodn. nor action. Troglitazone inhibited action rather than
prodn. of TNF-.alpha. in vivo. In vitro troglitazone (10⁻⁴ mol/l)
significantly reduced cytolytic activity of TNF-.alpha. against LM cells.
These results indicate that gliclazide and troglitazone have inhibitory
effect on TNF-.alpha..

RE.CNT 41

RE

- (3) Dawson, D; Neurosci Lett 1996, V218, P41 CA
- (4) Eisenhut, T; Immunopharmacology 1993, V26, P259 CA
- (5) Feinstein, R; J Biol Chem 1993, V268, P26055 CA
- (6) Ferner, R; Clin Pharmacokinet 1987, V12, P379 CA
- (7) Fujitani, B; Jpn J Pharmacol 1983, V33, P965 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 40 CA COPYRIGHT 2000 ACS

AN 130:61072 CA

TI Use of PPAR.gamma. agonists for inhibition of inflammatory cytokine
production

IN Seed, Brian; Jiang, Chengyu

PA The General Hospital Corporation, USA

SO PCT Int. Appl., 25 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9857631	A1	19981223	WO 1998-US12563	19980617
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	US 5925657	A	19990720	US 1997-878406	19970618
	AU 9881471	A1	19990104	AU 1998-81471	19980617

PRAI US 1997-878406 19970618

WO 1998-US12563 19980617

AB Methods are disclosed for reducing or preventing cytokine prodn. assocd. with an inflammatory response, involving administering to a mammal a therapeutically effective amt. of a thiazolidinedione PPAR.gamma.

agonist.

RE.CNT 2

RE

- (1) Ohsumi; Endocrinology 1994, 5, P2279
- (2) Peraldi; J Clin Invest 1997, 7, P1863

L7 ANSWER 21 OF 40 CA COPYRIGHT 2000 ACS

AN 130:75735 CA

TI Synthesis and biological activity of novel thiazolidinediones

AU Prabhakar, C.; Madhusudhan, G.; Sahadev, K.; Reddy, Ch. Maheedhara; Sarma,

M. R.; Reddy, G. Om; Chakrabarti, R.; Rao, C. Seshagiri; Kumar, T.

Dileep;

Rajagopalan, R.

CS Department of Process Research and Development, Department of Pharmacology, Dr. Reddy's Research Foundation, Hyderabad, 500 050, India

SO Bioorg. Med. Chem. Lett. (1998), 8(19), 2725-2730

CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier Science Ltd.

DT Journal

LA English

AB Novel compds. having a dual pharmacophore were synthesized and evaluated for their insulin sensitizing and anti-inflammatory properties in different animal models.

RE.CNT 16

RE

(8) Drummer, O; J Anal Toxicol 1993, V17, P225 CA

(9) Harrison, I; J Med Chem 1970, V13, P203 CA

(10) Horikoshi, H; Annu Rep Sankyo Res Lab 1994, V46, P1 CA

(11) Lohray, B; Biorg Med Chem Lett 1997, V7, P785 CA

(12) Nan, Z; Zhongguo Yiyao Gongye Zazhi 1994, V25, P133 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 40 CA COPYRIGHT 2000 ACS

AN 129:229515 CA

TI The short- and long-term effects of tumor necrosis factor-.alpha. and BRL 49653 on peroxisome proliferator-activated receptor (PPAR).gamma.2 gene expression and other adipocyte genes

AU Edelstein Rosenbaum, Susan; Greenberg, Andrew S.

CS The USDA Human Nutrition Research Center on Aging at Tufts, Tupper Medical

Research Institute New England Medical Center Boston, University and Division of Endocrinology, Boston, MA, 02111, USA

SO Mol. Endocrinol. (1998), 12(8), 1150-1160

CODEN: MOENEN; ISSN: 0888-8809

PB Endocrine Society
DT Journal
LA English
AB Expression of tumor necrosis factor-.alpha. (TNF.alpha.) in adipocytes
has been reported to correlate with insulin resistance assocd. with obesity. The thiazolidinediones such as BRL 49653 have been reported to improve insulin sensitivity in obese animals and humans. Although its exact mechanism of action is not known, BRL 49653 has been shown to antagonize some of the inhibitory actions of TNF.alpha.. BRL 49653 binds and activates the peroxisome proliferator-activated receptor (PPAR.gamma.2), an important nuclear transcription factor in adipocyte differentiation; however, its regulation of PPAR.gamma.2 in differentiated adipocytes is unknown. Here, the authors find that BRL 49653 blocked the ability of TNF.alpha. to down-regulate the expression and transcription of several adipocyte genes, but BRL 49653 did not prevent TNF.alpha. from down-regulating PPAR.gamma.2. Moreover, BRL 49653 alone initially decreased the expression of PPAR.gamma.2 mRNA and protein greatly. After 24 h of treatment in 3T3-L1 adipocytes, BRL 49653 down-regulated PPAR.gamma.2 by greater than 90% and potentiated the decrease of PPAR.gamma.2 mRNA by TNF.alpha. at this time. These unexpected results prompted the authors to repeat the expts. for a longer time to det. whether BRL 49653 would continue to down-regulate PPAR.gamma.2. With prolonged BRL 49653 treatment, PPAR.gamma.2 mRNA expression was not decreased as greatly, and the protein levels were decreased 20-30% below control at 72 h compared to 90% at 24 h. Although BRL 49653 continued to prevent the inhibitory effects of TNF.alpha. on perilipin and aP2 mRNA,
by 72 h, BRL 49653 was not as potent an inhibitor of TNF.alpha.'s down-regulation of perilipin protein. Since PPAR.gamma.2 protein was
more abundant at this time, these results suggest that the level of PPAR.gamma.2 protein is not the sole factor that regulates the transcriptional control by BRL 49653.

L7 ANSWER 23 OF 40 CA COPYRIGHT 2000 ACS
AN 129:407 CA
TI BRL 49653 blocks the lipolytic actions of tumor necrosis factor-.alpha.:
A potential new insulin-sensitizing mechanism for thiazolidinediones
AU Souza, Sandra C.; Yamamoto, Mia T.; Franciosi, Mark D.; Lien, Ping;
Greenberg, Andrew S.
CS Jean Mayer Human Nutrition Research Center on Aging, Tufts University,
Boston, MA, 02111, USA
SO Diabetes (1998), 47(4), 691-695
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB Thiazolidinediones (TZDs) such as BRL 49653 are a class of antidiabetic agents that are agonists for the peroxisome proliferator-activated nuclear receptor (PPAR-.gamma.2). In vivo, TZDs reduce circulating levels of free fatty acids (FFAs) and ameliorate insulin resistance in individuals with obesity and NIDDM. Adipocyte prodn. of TNF-.alpha. is proposed to play a role in the development of insulin resistance, and because BRL 49653 has been shown to antagonize some of the effects of TNF-.alpha., we examd.
the effects of TNF-.alpha. and BRL 49653 on adipocyte lipolysis. After a 24-h incubation of TNF-.alpha. (10 ng/mL) with 3T3-L1 adipocytes, glycerol release increased by .apprx.7-fold, and FFA release increased by .apprx.44-fold. BRL 49653 (10 .mu.mol/l) reduced TNF-.alpha.-induced glycerol release by .apprx.50% ($P < 0.001$) and FFA release by .apprx.90%

($P < 0.001$). BRL 49653 also reduced glycerol release by .apprx.50% in adipocytes pretreated for 24 h with TNF-.alpha.. Prolonged treatment (5 days) with either BRL 49653 or another PPAR-.gamma.2 agonist, 15-d-.DELTA.-12,14-prostaglandin J2 (15-d.DELTA.PGJ2), blocked TNF-.alpha.-induced glycerol release by .apprx.100%. Catecholamine (isoproterenol)-stimulated lipolysis was unaffected by BRL 49653 and 15-d.DELTA.PGJ2. BRL 49653 partially blocked the TNF-.alpha.-mediated redn. in protein levels of hormone-sensitive lipase and perilipin A, two proteins involved in adipocyte lipolysis. These data suggest a novel pathway that may contribute to the ability of the TZDs to reduce serum

FFA

and increase insulin sensitivity.

L7 ANSWER 24 OF 40 CA COPYRIGHT 2000 ACS

AN 128:162759 CA

TI Pioglitazone time-dependently reduces tumor necrosis factor-.alpha. level in muscle and improves metabolic abnormalities in Wistar fatty rats

AU Murase, K.; Odaka, H.; Suzuki, M.; Tayuki, N.; Ikeda, H.

CS Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., Osaka, 532, Japan

SO Diabetologia (1998), 41(3), 257-264

CODEN: DBTGAJ; ISSN: 0012-186X

PB Springer-Verlag

DT Journal

LA English

AB To evaluate the relationship between tumor necrosis factor-.alpha. ($TNF\text{-}\alpha$) level in muscle and metabolic abnormalities in obesity and diabetes mellitus, pioglitazone, a novel insulin-sensitizing agent, was administered to Wistar fatty rats and time-dependent changes in muscle $TNF\text{-}\alpha$. content and plasma indicators of diabetes and obesity were measured. Wistar fatty rats were hyperglycemic, hyperlipidemic, and hyperinsulinemic, and their blood plasma and muscle $TNF\text{-}\alpha$. levels were 2 or more times higher than those in normal lean rats at 16 wk of age. When pioglitazone was administered to fatty rats at a dose of 3 mg/kg/day, the plasma triglyceride level and $TNF\text{-}\alpha$. levels in plasma and muscle decreased time-dependently, and reached the levels of lean

rats

within 4 days. Plasma glucose and insulin levels also decreased time-dependently with pioglitazone, but on day 4, these levels were still much higher than the levels in lean rats. Neutral sphingomyelinase (SMase) activity in muscle of fatty rats was 2 .times. higher than that

in

lean rats and was lowered to the level of that in lean rats by 4 days' pioglitazone administration. The plasma leptin level in fatty rats was 8 .times. higher than that in lean rats, but pioglitazone did not affect

the

level during the 4-day administration period. These results suggest that an increase in $TNF\text{-}\alpha$. prodn. and subsequent activation of SMase in muscle leads to metabolic abnormalities in obesity and diabetes and that antidiabetic activity of pioglitazone is deeply assocd. with the suppression of $TNF\text{-}\alpha$. prodn.

L7 ANSWER 25 OF 40 CA COPYRIGHT 2000 ACS

AN 128:188444 CA

TI PPAR-.gamma. agonists inhibit production of monocyte inflammatory cytokines

AU Jiang, Chengyu; Ting, Adrian T.; Seed, Brian

CS Dep. Molecular Biol., Massachusetts General Hosp., Boston, MA, 02114, USA

SO Nature (London) (1998), 391(6662), 82-86

CODEN: NATUAS; ISSN: 0028-0836

PB Macmillan Magazines

DT Journal

LA English

AB The peroxisome proliferator-activated receptor-.gamma. (PPAR-.gamma.) is a

member of the nuclear receptor family of transcription factors, a large and diverse group of proteins that mediate ligand-dependent transcriptional activation and repression. Expression of PPAR-.gamma. is an early and pivotal event in the differentiation of adipocytes. Several agents that promote differentiation of fibroblast lines into adipocytes have been shown to be PPAR-.gamma. agonists, including several prostanoids, of which 15-deoxy-.DELTA.12,14-prostaglandin J2 is the most potent, as well as members of a new class of oral antidiabetic agents,

the thiazolidinediones, and a variety of non-steroidal anti-inflammatory drugs

(NSAIDs). Here we show that PPAR-.gamma. agonists suppress monocyte elaboration of inflammatory cytokines at agonist concns. similar to those effective for the promotion of adipogenesis. Inhibition of cytokine prodn. may help to explain the incremental therapeutic benefit of NSAIDs obstd. in the treatment of rheumatoid arthritis at plasma drug concns. substantially higher than are required to inhibit prostaglandin G/H synthase (cyclooxygenase).

L7 ANSWER 26 OF 40 CA COPYRIGHT 2000 ACS

AN 127:326063 CA

TI Thiazolidinediones block tumor necrosis factor-.alpha.-induced inhibition of insulin signaling

AU Peraldi, Pascal; Xu, Min; Spiegelman, Bruce M.

CS Dana-Farber Cancer Institute and Department of Cell Biology, Harvard Medical School, Boston, MA, 02115, USA

SO J. Clin. Invest. (1997), 100(7), 1863-1869

CODEN: JCINAO; ISSN: 0021-9738

PB Rockefeller University Press

DT Journal

LA English

AB TNF-.alpha. has been shown to be an important mediator of insulin resistance linked to obesity. This cytokine induces insulin resistance, at least in part, through inhibition of the tyrosine kinase activity of the insulin receptor. Recently, a new class of compds., the antidiabetic thiazolidinediones (TZDs), has been shown to improve insulin resistance

in obesity and non-insulin-dependent diabetes mellitus in both rodents and man. Here the authors show that TZDs have powerful effects on the ability

of TNF-.alpha. to alter the most proximal steps of insulin signaling, including tyrosine phosphorylation of the insulin receptor and its major substrate, IRS-1, and activation of PI3-kinase. Troglitazone or pioglitazone essentially eliminate the redn. in tyrosine phosphorylation of IR and IRS-1 caused by TNF-.alpha. in fat cells, even at relatively high doses (25 ng/mL). That this effect of TZDs operates through activation of the nuclear receptor PPAR.gamma./RXR complex is shown by

the

fact that similar effects are obstd. with other PPAR.gamma./RXR ligands such as 15 deoxy .DELTA.12,14PGJ2 and LG268. The TZDs do not inhibit all TNF-.alpha. signaling in that the transcription factor NF-.kappa.B is still induced well. These data indicate that TZDs can specifically block certain actions of TNF-.alpha. related to insulin resistance, suggesting that this block may contribute to their antidiabetic actions.

L7 ANSWER 27 OF 40 CA COPYRIGHT 2000 ACS

AN 128:18583 CA

TI TNF-.alpha.-induced insulin resistance in vivo and its prevention by troglitazone

AU Miles, Philip D. G.; Romeo, Oreste M.; Higo, Katsuya; Cohen, Aaron; Rafaat, Karim; Olefsky, Jerrold M.

CS Department of Surgery, University of California, San Diego, CA, 92103,

USA

SO Diabetes (1997), 46(11), 1678-1683

CODEN: DIAEAZ; ISSN: 0012-1797

PB American Diabetes Association
DT Journal
LA English
AB Tumor necrosis factor (TNF)-.alpha. may play a role in the insulin resistance of obesity and NIDDM. Troglitazone is a new orally active hypoglycemic agent that has been shown to ameliorate insulin resistance and hyperinsulinemia in both diabetic animal models and NIDDM subjects. To det. whether this drug could prevent the development of TNF-.alpha.-induced insulin resistance, glucose turnover was assessed in rats infused with cytokine and pretreated with troglitazone. Normal male Sprague-Dawley rats were fed normal powd. food with or without troglitazone as a food admixt. (0.2%). After .apprx.10 days, rats were infused with TNF-.alpha. for 4-5 days, producing a plasma concn. of 632 pg/mL. In vivo insulin action was measured by the euglycemic-hyperinsulinemic clamp technique at a submaximal (24 .mu.mol .cntdot.
kg-1 .cntdot. min-1) and maximal insulin infusion rate (240 .mu.mol .cntdot. kg-1 .cntdot. min-1). TNF-.alpha. infusion resulted in a pronounced redn. in submaximal insulin-stimulated glucose disposal rate (GDR) (97 vs. 141 .mu.mol .cntdot. kg-1 .cntdot. min-1), maximal GDR (175 vs. 267 .mu.mol .cntdot. kg-1 .cntdot. min-1), and in insulin receptor-tyrosine kinase activity (IR-TKA) (248 vs. 406 fmol ATP/fmol IR). It also led to a marked increase in basal insulin (90 vs. 48 pmol/l) and free fatty acid (FFA) concn. (2.56 vs. 0.87 mmol/l). Troglitazone treatment completely prevented the TNF-.alpha.-induced decline in submaximal GDR (133 vs. 141 .mu.mol .cntdot. kg-1 .cntdot. min-1, NS) and maximal GDR (271 vs. 267 .mu.mol .cntdot. kg-1 .cntdot. min-1, NS). The hyperlipidemia was partially cor. by troglitazone (1.53 vs. 0.87 mmol/l), while IR-TKA and insulin concn. remained unaffected by the drug. Troglitazone restores insulin action possibly by lowering the FFA concn. of the blood and/or by stimulating glucose uptake at an intracellular point distal to insulin receptor autophosphorylation in muscle. If TNF-.alpha. plays a role in the development of the obesity/NIDDM syndrome, troglitazone may prove useful in its treatment.

L7 ANSWER 28 OF 40 CA COPYRIGHT 2000 ACS
AN 127:214914 CA
TI Salt sensitivity of OLETF rats and hypotensive effect of troglitazone
AU Ohashi, Minoru; Takei, Izumi; Saruta, Takao
CS Naika, Keio Gijuku Daigaku, Tokyo, 160, Japan
SO Diabetes Front. (1997), 8(4), 504
CODEN: DIFREZ; ISSN: 0915-6593
PB Medikaru Rebyusha
DT Journal
LA Japanese
AB OLETF rats fed a diet contg. 8.3% NaCl showed significantly higher systolic pressure and had a tendency of higher blood TNF-.alpha. level than controls fed a 0.3% NaCl-contg. diet. A diet contg. 0.2% troglitazone lowered the systolic pressure and TNF-.alpha. concn. of male OLETF rats in the both groups, suggesting involvement of TNF-.alpha. in antihypertensive activity of troglitazone.

L7 ANSWER 29 OF 40 CA COPYRIGHT 2000 ACS
AN 127:214970 CA
TI Pioglitazone and metformin reverse insulin resistance induced by tumor necrosis factor-alpha in liver cells
AU Solomon, Solomon S.; Mishra, S. K.; Cwik, C.; Rajanna, B.; Postlethwaite, A. E.
CS Research Medical Services, VAMC, Memphis, TN, 38104, USA
SO Horm. Metab. Res. (1997), 29(8), 379-382
CODEN: HMMRA2; ISSN: 0018-5043
PB Thieme
DT Journal

LA English
 AB Tumor necrosis factor-.alpha. (TNF-.alpha.) was recently implicated as a cause of insulin resistance (IR) in obesity and non-insulin dependent diabetes mellitus (NIDDM). To examine mechanisms involved, IR was induced in H-411 E cells with graded doses of TNF-.alpha. and measured the ability of insulin (INS) to stimulate both calmodulin (CaM) mRNA and glucose utilization. With TNF-.alpha. concn. at 1 ng/mL and 104 .mu.U/mL INS, metformin 10 .mu.M, and pioglitazone 1.5 .mu.M, reversed the IR induced by TNF-.alpha. restoring biol. response to 100% of INS effect alone. Furthermore, comparable results were obtained with glucose utilization/oxidn. expts. in the H-411E cells using glucose U-14C, trapping 14CO₂ release in a hyamine filter and extg. 14C labeled lipids with Dole's reagent. In conclusion, these data add scientific support for the use of both metformin and pioglitazone in treatment of IR in NIDDM patients and support a rationale for use of these drugs alone, and in conjunction with oral agents and/or INS treatment.

L7 ANSWER 30 OF 40 CA COPYRIGHT 2000 ACS
 AN 126:166481 CA
 TI Combination of a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for the treatment of inflammations
 IN Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
 PA G.D. Searle & Co., USA
 SO PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9641645	A1	19961227	WO 1996-US9905	19960611
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2224563	AA	19961227	CA 1996-2224563	19960611
	AU 9662694	A1	19970109	AU 1996-62694	19960611
	EP 833664	A1	19980408	EP 1996-921477	19960611
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,				
FI	JP 11507669	T2	19990706	JP 1996-503237	19960611
PRAI	US 1995-489415		19950612		
	WO 1996-US9905		19960611		
OS	MARPAT 126:166481				

AB Combinations of a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist are described for treatment of inflammation and inflammation-related disorders. The cyclooxygenase-2 inhibitors were prep'd. Also, formulations for the drug combination are described.

L7 ANSWER 31 OF 40 CA COPYRIGHT 2000 ACS
 AN 126:166479 CA
 TI Compositions comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders
 IN Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
 PA G.D. Searle and Co., USA
 SO PCT Int. Appl., 73 pp.
 CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9641626	A1	19961227	WO 1996-US10106	19960611
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2224517	AA	19961227	CA 1996-2224517	19960611
	AU 9661117	A1	19970109	AU 1996-61117	19960611
	EP 833622	A1	19980408	EP 1996-918465	19960611
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,				

FI

JP 11507670 T2 19990706 JP 1996-503273 19960611

PRAI US 1995-489472 19950612
WO 1996-US10106 19960611

OS MARPAT 126:166479

AB Combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor are described for treatment of inflammation and inflammation-related disorders. Prepn. of e.g. 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is described., as

are pharmaceutical formulations and activity against collagen-induced arthritis in mice.

L7 ANSWER 32 OF 40 CA COPYRIGHT 2000 ACS

AN 122:204910 CA

TI Antidiabetic thiazolidinediones block the inhibitory effect of tumor necrosis factor-.alpha. on differentiation, insulin-stimulated glucose uptake, and gene expression in 3T3-L1 cells

AU Szalkowski, Deborah; White-Carrington, Sylvia; Berger, Joel; Zhang, Bei
CS Dep. Mol. Endocrinology, Merck Res. Lab., Rahway, NJ, 07065, USA

SO Endocrinology (1995), 136(4), 1474-81
CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

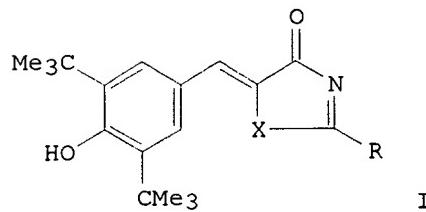
AB Tumor necrosis factor-.alpha. (TNF.alpha.) is a cytokine implicated in the

development of septic shock, cachexia, and other pathol. states. Recent studies indicated a direct role for adipose expression of TNF.alpha. in obesity-linked insulin resistance and diabetes. Pioglitazone, CP-86,325 (CP), AD-5075, CS-045, ciglitazone, and englitazone are members of a new class of insulin-sensitizing thiazolidinedione derivs. with in vivo antidiabetic activities. To test whether these agents antagonize the effect of TNF.alpha., 3T3-L1 cells were induced to differentiate in the presence of TNF.alpha. with or without thiazolidinedione derivs. Incubation of 3T3-L1 cells with TNF.alpha. alone completely inhibited adipocyte conversion and expression of fatty acid-binding protein mRNA (mRNA). However, coincubation of TNF.alpha.-treated cells with CP (1 .mu.M), AD-5075 (1 .mu.M), pioglitazone (10 .mu.M), or CS-045 (10 .mu.M) blocked these effects. Long-term incubation of 3T3-L1 adipocytes with a low dose of TNF.alpha. (50 pM) significantly decreased the levels of the adipocyte/muscle-specific glucose transporter (GLUT4) and the CCAAT enhancer-binding protein mRNAs, but did not affect expression of the ubiquitously expressed glucose transporter (GLUT1) or lipoprotein lipase mRNAs. Incubation of 3T3-L1 adipocytes with TNF.alpha. also inhibited insulin-stimulated 2-deoxyglucose uptake as well as expression of GLUT4 protein. Furthermore, in 3T3-L1 adipocytes, incubation with TNF.alpha. attenuated the expression of fatty acid-binding protein mRNA in a time- and dose-dependent manner. These inhibitory effects were partially or completely blocked by coincubation of the cells with CP. These results

implicate that the insulin-sensitizing agents may exert their antidiabetic activities by antagonizing the inhibitory effects of TNF.alpha..

L7 ANSWER 33 OF 40 CA COPYRIGHT 2000 ACS
AN 121:292489 CA
TI Troglitazone prevents the inhibitory effects of inflammatory cytokines on insulin-induced adipocyte differentiation in 3T3-L1 cells
AU Ohsumi, Jun; Sakakibara, Sachiko; Yamaguchi, Junko; Miyadai, Kenji; Yoshioka, Shinji; Fujiwara, Toshihiko; Horikoshi, Hiroyoshi; Serizawa, Nobufusa
CS Biomedical Research Laboratories, Pharmacology Molecular Biology Research Laboratories, Tokyo, 140, Japan
SO Endocrinology (1994), 135(5), 2279-82
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
AB Tumor necrosis factor (TNF) is implicated in wasting syndromes and insulin resistance in chronic infection and obese-linked diabetes. TNF (10 ng/mL) inhibited adipocyte differentiation of 3T3-L1 cells, and in these TNF treated cells little insulin-stimulated glucose uptake was obsd. Treatment of 3T3-L1 cells with troglitazone (1-10 .mu.M) partially prevented this inhibitory effect of TNF on adipogenesis, and enhanced expression of C/EBP.alpha. and GLUT4, even in the presence of TNF. Troglitazone also prevented the inhibitory effects of interleukin-1, interleukin-6, and leukemia inhibitory factor, but not of transforming growth factor .beta. on adipocyte differentiation of 3T3-L1 cells. These effects might contribute to the antidiabetic effect of troglitazone in obese diabetic animals.

L7 ANSWER 34 OF 40 CA COPYRIGHT 2000 ACS
AN 120:244834 CA
TI Synthesis and biological evaluation of 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]oxazoles, -thiazoles, and -imidazoles: novel dual 5-lipoxygenase and cyclooxygenase inhibitors with antiinflammatory activity
AU Unangst, Paul C.; Connor, David T.; Cetenko, Wiaczeslaw A.; Sorenson, Roderick J.; Kostlan, Catherine R.; Sircar, Jagadish C.; Wright, Clifford D.; Schrier, Denis J.; Dyer, Richard D.
CS Parke-Davis Pharm. Res., Warner-Lambert Co., Ann Arbor, MI, 48105, USA
SO J. Med. Chem. (1994), 37(2), 322-8
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI



AB A variety of benzylideneoxazoles [I; X = O, R = SH, NHCN.cndot.choline, NHC(:NH)NH2.cndot.MeSO3H, OH.cndot.choline], -thiazoles [I; X = S, R = OH, SH, NH2.cndot.choline, SMe, NHMe, NMe2, NHOH, NMeOH, NHOMe, NMeOMe.cndot.HCl, NHCN, NHC(:NH)NH2.cndot.HCl, NHC(:NH)NMe2, NHCH2CH2NMe2, NHCH2CH2CH2CO2H], and -imidazoles [I; X = NMe, R = OH, SH,

NHCN, NHC(:NH)NH₂] derived from 2,6-di-tert-butylphenol were prepd. and evaluated as dual inhibitors of 5-lipoxygenase and cyclooxygenase in rat basophilic leukemia (RBL-1) cells. The target compds. exhibit varying degrees of selectivity toward the 2 enzymes. Several compds. are orally active in the rat carageenan footpad edema (CFE) and myobacterium footpad edema (MFE) antiinflammatory models. Structure-activity relationships

are discussed. From this work, (Z)-5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-2-imino-4-thiazolidinone methanesulfonate salt (CI-1004; I; X = S, R = NH₂.cntdot.MeSO₃H) was identified as a potent dual inhibitor of 5-lipoxygenase (IC₅₀ = 0.77 .mu.M) and cyclooxygenase (IC₅₀ = 0.39 .mu.M), with oral activity (ID₄₀ = 0.6 mg/kg) in the rat MFE model of inflammation.

L7 ANSWER 35 OF 40 CA COPYRIGHT 2000 ACS

AN 120:97018 CA

TI Altered gene expression for tumor necrosis factor-.alpha. and its receptors during drug and dietary modulation of insulin resistance

AU Hofmann, Cecilia; Lorenz, Kathryn; Braithwaite, Susan S.; Colca, Jerry R.;

Palazuk, Barbara J.; Hotamisligil, Goekhan S.; Spiegelman, Bruce M.

CS Res. Serv., Hines Vet. Adm. Hosp., Hines, IL, 60141, USA

SO Endocrinology (1994), 134(1), 264-70

CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

AB As obesity is a major risk factor for noninsulin-dependent diabetes mellitus, adipose tissue may generate a mediator that influences the activity of insulin on various target tissues. Recent evidence suggests that a cytokine, tumor necrosis factor-.alpha. (TNF-.alpha.), may serve this role. This study investigates whether the expression of TNF.alpha. and its receptors is modulated during drug treatment to reduce insulin resistance. The effects of moderate wt. loss by dietary restriction were also examd. The authors show here that a marked induction of TNF.alpha. mRNA occurs in adipose tissues from a mouse model of obesity-linked diabetes (KKAy) compared to that in nondiabetic mice (C57). Likewise,

RNA

transcripts encoding TNF R2 receptors (p75) were significantly increased in fat tissues of the obese diabetic animals. In muscle from these diabetic animals, RNA transcripts encoding both TNR R1 (p55) and R2 were significantly elevated, although R2 transcript abundance was less elevated

than in fat. The authors also obsd. that the overexpression of mRNA for TNF.alpha. and both of its receptors could be at least partly normalized by treatment of the diabetic animals with the insulin-sensitizing agent pioglitazone. Treating of the obese diabetic animals by food restriction reduced the expression of mRNA for TNF R2 in muscle, but not fat. These results clearly indicate that gene expression for the TNF systems can be regulated by an insulin-sensitizing drug and redn. of body wt. Such findings support a role for this cytokine in the insulin-resistant diabetic state and show its modulation by therapies that reverse the disorder.

L7 ANSWER 36 OF 40 CA COPYRIGHT 2000 ACS

AN 119:95529 CA

TI 5-hydroxy-2-pyrimidinylmethylen derivatives useful as antiinflammatory agents

IN Belliotti, Thomas Richard; Connor, David Thomas; Kostlan, Catherine Rose

PA Warner-Lambert Co., USA

SO PCT Int. Appl., 58 pp.

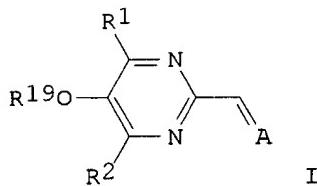
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9305039	A1	19930318	WO 1992-US7412	19920902
	W: AU, CA, CS, FI, HU, JP, KR, NO, RU RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
	US 5270319	A	19931214	US 1992-909850	19920707
	AU 9225782	A1	19930405	AU 1992-25782	19920902
	US 5348957	A	19940920	US 1993-103462	19930806
PRAI	US 1991-756400		19910909		
	US 1992-909850		19920707		
	WO 1992-US7412		19920902		
OS	MARPAT 119:95529				
GI					



AB The title compds. I (R1,R2 = H, alkyl; R19 = H, acetyl; A = heterocyclic group) are claimed. I are inflammation inhibitors and pharmaceuticals contg. I and a nonsteroidal inflammation inhibitor are claimed. The use of I for the treatment of conditions affected by inhibition of 5-lipoxygenase or cyclooxygenase is claimed. A mixt. of 4,6-bis(1,1-dimethylethyl)-5-[(2-methoxyethoxy)methylene]-2-pyrimidinecarboxaldehyde and rhodanine and .beta.-alanine in acetic acid was refluxed to give 5-[4,6-bis(1,1-dimethylethyl)-5-[(2-methoxyethoxy)methoxy]-2-pyrimidinyl]methylene]-2-thioxo-4-thiazolidinone.

L7 ANSWER 37 OF 40 CA COPYRIGHT 2000 ACS

AN 120:298540 CA

TI Oxazole, thiazole, and imidazole derivatives of 2,6-di-tert-butylphenol as

dual 5-lipoxygenase and cyclooxygenase inhibitors

AU Unangst, Paul C.; Connor, David T.; Cetenko, Wiaczeslaw A.; Sorenson, Roderick J.; Sircar, Jagadish C.; Wright, Clifford D.; Schrier, Denis J.; Dyer, Richard D.

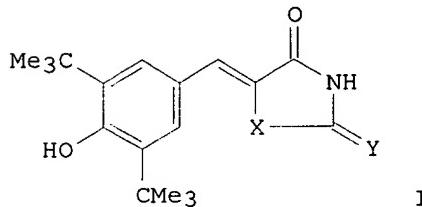
CS Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Ann Arbor, MI, 48105, USA

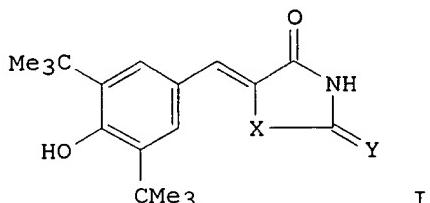
SO Bioorg. Med. Chem. Lett. (1993), 3(8), 1729-34
CODEN: BMCLE8; ISSN: 0960-894X

DT Journal

LA English

GI





AB Benzylidene di-tert-butylphenols contg. oxazole, thiazole, and imidazole substituents I (X = O, S, NMe; Y = NH, O, S) are dual inhibitors of 5-lipoxygenase and cyclooxygenase with IC₅₀ values <5 .mu.M. The oxazole and thiazole analogs exhibit oral antiinflammatory activity.

L7 ANSWER 38 OF 40 CA COPYRIGHT 2000 ACS

AN 118:38921 CA

TI Preparation of 2-substituted thiazolidinone, oxazolidinone, and imidazolidinone derivatives of fenamates as antiinflammatory agents

IN Belliotti, Thomas R.; Boschelli, Diane H.; Connor, David T.; Kostlan, Catherine R.

PA Warner-Lambert Co., USA

SO U.S., 12 pp.

CODEN: USXXAM

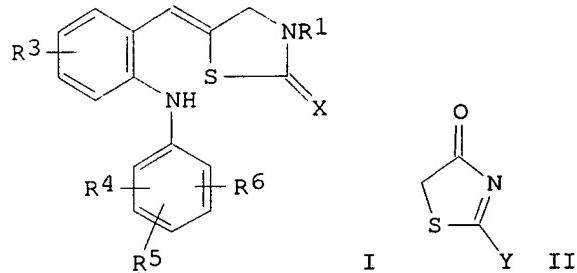
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5143929	A	19920901	US 1991-697822	19910509
OS	MARPAT 118:38921				

GI



AB Title compds. I [X = O, S, HN; R1 = alkyl, R2O₂CCH₂ wherein R2 not defined; R3-R6 = H, halo, F₃C, alkyl, NC, HO, alkoxy, O₂N, R8R7N wherein R7, R8 = H, alkyl, acyl, (O)nS wherein x = 0-2] and II [Y = HO, HS, H₂N, R9S wherein R9 = alkyl, R10O₂CCH₂ wherein R10 = H, alkyl, R9(O)xS wherein w = 0-2, R10R9N, etc., (no examples or claims for oxazolididine or imidazolidinone] and salt thereof, are prep'd. To 2-[{(2,6-dichloro-3-methylphenyl)amino]benzaldehyde at room temp. and 3-methylrhodanine in AcOH was added .beta.-alanine and refluxed to give (Z)-I (X = S, R1 = Me, R4 = 2-Cl, R5 = 6-Cl, R6 = 3-Me) (III). In a test for antiinflammatory activity III at 10 .mu.M showed 100% inhibition of LTB₄ formation.

L7 ANSWER 39 OF 40 CA COPYRIGHT 2000 ACS

AN 114:122357 CA

TI Preparation of 5-(4-hydroxyphenyl)-2-thioxo-4-thiazolidinones and related compounds as antinflammatories

IN Panetta, Jill Ann

PA Lilly, Eli, and Co., USA

SO Eur. Pat. Appl., 69 pp.

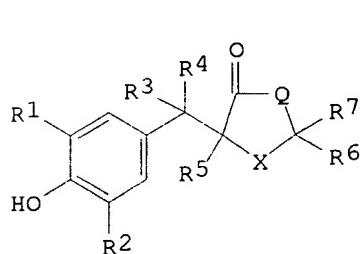
CODEN: EPXXDW

DT Patent

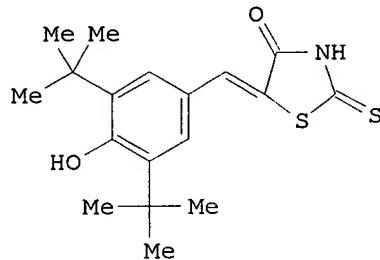
LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 391644	A2	19901010	EP 1990-303510	19900402
	EP 391644	A3	19910424		
	EP 391644	B1	19960619		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE				
	CA 2013599	AA	19901007	CA 1990-2013599	19900402
	ZA 9002520	A	19911224	ZA 1990-2520	19900402
	AT 139531	E	19960715	AT 1990-303510	19900402
	ES 2088965	T3	19961001	ES 1990-303510	19900402
	AU 9052934	A1	19901011	AU 1990-52934	19900405
	AU 629322	B2	19921001		
	JP 02290862	A2	19901130	JP 1990-92981	19900406
	HU 56356	A2	19910828	HU 1990-2115	19900406
	US 5356917	A	19941018	US 1993-111226	19930824
	US 5691367	A	19971125	US 1996-733909	19961018
PRAI	US 1989-335063	19890407			
	US 1985-764160	19850809			
	US 1986-869488	19860602			
	US 1987-114278	19871027			
	US 1989-304919	19890201			
	US 1990-504147	19900403			
	US 1992-839693	19920220			
	US 1993-111226	19930824			
	US 1994-290664	19940815			
OS	MARPAT 114:122357				
GI					



I



II

AB The title compds. (I; R1, R2 = H, alkyl, alkoxy, alkylcarbonyloxyalkyl;
R3
= H, alkyl; R4, R5 = H; R4R5 = bond; R5, R6 = H, or one of R6, R7 = H, the
other = OH, SMe; R5R6 = S, O; X = SON; n = 0-2), were prep'd. Thus, a
mixt. of 3,5-di-tert-butyl-4-hydroxybenzaldehyde, rhodanine, and NaOAc
was refluxed 23 h in HOAc to give title compd. II. II at 50 mg/kg orally in
rats gave 100% inhibition of collagen-induced arthritis. I also
prevented
ischemic-induced brain damage in rats and prolonged the lives of
dystrophic mice. Pharmaceutical I formulations are given.

L7 ANSWER 40 OF 40 CA COPYRIGHT 2000 ACS

AN 112:235298 CA

TI Preparation of (arylmethylenyl)thiazolidinones, -imidazolidinones and
-oxazolidinones as antiinflammatory agents and antiallergy agents

IN Cetenko, Wiaczeslaw Antin; Connor, David Thomas; Sorenson, Roderick
Joseph; Unangst, Paul Charles; Stabler, Stephen Russell

PA Warner-Lambert Co., USA

SO Eur. Pat. Appl., 53 pp.

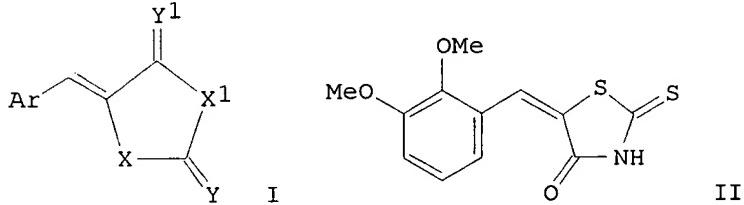
CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 343643	A2	19891129	EP 1989-109406	19890524
	EP 343643	A3	19900321		
	EP 343643	B1	19940323		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AU 8935058	A1	19891130	AU 1989-35058	19890522
	AU 626863	B2	19920813		
	ZA 8903834	A	19910130	ZA 1989-3834	19890522
	DK 8902520	A	19891126	DK 1989-2520	19890524
	FI 8902522	A	19891126	FI 1989-2522	19890524
	NO 8902083	A	19891127	NO 1989-2083	19890524
	JP 02062864	A2	19900302	JP 1989-129047	19890524
	JP 2899309	B2	19990602		
	EP 565135	A1	19931013	EP 1993-108883	19890524
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AT 103175	E	19940415	AT 1989-109406	19890524
	ES 2063073	T3	19950101	ES 1989-109406	19890524
	CA 1340247	A1	19981215	CA 1989-600509	19890524
	KR 9702228	B1	19970226	KR 1989-7006	19890525
	US 5208250	A	19930504	US 1991-702132	19910513
	US 5306822	A	19940426	US 1992-988562	19921210
	US 5464856	A	19951107	US 1994-185748	19940124
PRAI	US 1988-198528		19880525		
	US 1989-334346		19890410		
	EP 1989-109406		19890524		
	US 1989-375794		19890705		
	US 1991-702132		19910513		
	US 1992-988562		19921210		
OS	MARPAT 112:235298				
GI					



AB The title compds [I; Ar = naphthyl, benzofuryl, benzothienyl, thieryl, indolyl, furyl, pyridyl, (substituted) Ph; Y, Y1 = S, O; X = S, O, NH, NMe; X1 = NH, NMe], cyclooxygenase and 5-lipoxygenase inhibitors, were prep'd. Thus, a mixt. of 2,3-(MeO)2C6H4CHO, rhodanine, and NaOAc was refluxed 4 h in HOAc to give (phenylmethylene)rhodanine deriv. II. I at 33 .mu.M gave up to 100% inhibition of ragweed/housedust-induced release of histamine from leukocytes of allergic donors.